PATENT
1261-0156PUS1

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Hiroyuki OSADA et al.	Conf.:	6909
Appl. No.:	10/516,743	Group:	1626
Filed:	May 26, 2005	Examiner:	Chung, S.L.
For:	NOVEL COMPOUND HAVING ANTITUMOR ACTIVITY AND PROCESS FOR PRODUCING THE SAME		

SECOND DECLARATION OF DR. HIDEAKI KAKEYA SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

I, Dr. Hideaki Kakeya of the Antibiotics Lab, Discovery Research Institute, RIKEN Japan, do hereby declare the following:

I have attached a copy of my current curriculum vitae to this Declaration.

I am presently a visiting Professor, Antibiotics Lab, Advanced Science Institute, RIKEN and have worked in the field of the present invention for 15 years.

I am familiar with the above referenced patent application and the area of science dealing with identification of novel compounds for use as antitumor drug candidates and drugs. I am also well versed in the use of antitumor agents for treatment of cancer.

I am familiar with the subject matter of the above-identified U.S. patent application, including the present claims, the Office Actions of November 24, 2006 and February 26, 2009, and the Hayashi and Kuramochi references cited against the claims. I am also familiar with the Nagumo (2004) reference cited by the Examiner in the February 26, 2009 Office Action.

The following comments are offered in support of the patentability of the instant invention.

The Examiner states in the November 24, 2006 Office Action that the invention of this application (i.e. 10/516,743; "'743") is obvious. The Examiner refers then to the Hayashi and Narasaka references (Chemistry Letters (1998) pages 313-314) and states that because the Hayashi and Naraska composition has a methyl group in the R position, adjacent homologues of CO_2R (for example ethyl, propyl, etc.) would be expected to work the same without evidence to the contrary.

In order to provide the unexpected results required by the Examiner, I previously described the following experiment.

To compare the action of the Epolactaene drug of Hayashi and Narasaka and the compound of the '743 application where R is t-BU in general formula I, a series of dilutions was made for each compound. An aliquot from each dilution was added to human neuroblastoma SH-SY5Y cells that were cultured in DMEM medium containing 5% fetal bovine serum. The cells were then cultured at 37°C under a 5% carbon dioxide atmosphere for 48 hours. A MTT (3-(4,5-dimethly-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide) reagent was then added and the cells further cultured for another 2 to 4 hours. To calculate the survival ratio, absorbance at 570 nm was measured in each case and the 50% growth-inhibition concentration determined.

The results indicated that Epolactaene has a 50% growth-inhibition concentration of 2.0 µg/ml. On the other hand, the compound of the '743 application where R is t-BU in general formula I has a 50% growth-inhibition concentration of 0.4 µg/ml. In other words, the compound of the '743 application was 5 times more efficacious in killing the neuroblastoma cells than was Hyashi and Narasaka' Epolactaene. This is important because administering a lower drug dosage to a patient to obtain the same effect drastically reduces any potential side-effects. Thus, the compound of the '743 application is superior to Epolactaene as an antitumor agent.

The Examiner indicates in the February 26, 2009 Office Action that my previous Declaration, dated March 31, 2007, is not sufficient evidence of unobviousness of the

present invention because it does not specifically state that a five-fold difference in efficacy of inhibition of growth of neuroblastoma cells is unpredictable.

In reaching this conclusion, the Examiner argues partly that Nagumo (2004) teaches a Structure Activity Relation (SAR) for the compound of the present invention that instructs that it is the "heterocyclic ring or lactam ring" that provides most of the activity of the compound. However, I note that Nagumo was published in 2004, almost two years after the priority date of the above-identified application, and therefore the teachings of the SAR were not available to guide one of ordinary skill in the art at the time the present invention was made.

Kuramochi reference (Tetrahedron Letters 40 (1999) 7371-7374) teaches that the characteristic features of epolactaene include the highly functionalized α,β-epoxy-γ-lactam core and the conjugated triene moiety in the side chain (page 7371, first paragraph). One of ordinary skill in the art who reads Kuramochi would expect that epoxy ring, lactam ring, or triene moiety in the compound is important for the activity. Thus, one of ordinary skill in the art would not have modified the R group in the compound to increase the activity.

Moreover, the effects of the compound with the bulky t-Bu group compared with the smaller methyl group are unpredictable in general.

Therefore, a five-fold difference in efficacy shown in my previous Declaration is unpredictable.

For all of the reasons set forth above, contrary to the assertion of the Examiner, the result of a five-fold better efficacy of inhibition of neuroblastoma growth is unpredictable and unexpected by one of ordinary skill in the art.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: May 25, 2009

Dr. Hideaki Kakeya